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Dissertation of Doctor of Philosophy

**Effect of Resistance Exercise on Physical Frailty and
Cognitive Function in Elderly with Cognitive Frailty**

**저항성 운동이 인지노쇠 노인들의 신체적 노쇠와
인지기능에 미치는 영향**

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ABSTRACT

The physical phenotypes of frailty and cognitive impairment are interrelated, and share several common pathophysiological mechanisms with physical frailty. The concept of “cognitive frailty” was proposed to stimulate research in this field. The new construct “cognitive frailty” is defined by the presence of both physical frailty and cognitive impairment (clinical dementia rating score = 0.5) in the absence of dementia. It is characterized by concurrent physical frailty and potentially reversible cognitive impairment. Consequently, the objective of this study was to determine the effect of high-speed resistance exercise training on cognitive function and physical performance in older adults with cognitive frailty. Second, examined the association between amyloid- β accumulation in the brain using a brain imaging biomarker and physical frailty parameters (weight loss, weakness, exhaustion, slowness, and low physical activity) in older adults with mild cognitive impairment (MCI) and cognitive frailty. Our results revealed that high-speed resistance exercise resulted in significant improvement in cognitive function (processing speed and executive function, both $p \leq 0.05$), physical function (SPPB, TUG, gait speed, both $p \leq 0.05$), and muscle strength (grip strength, knee extension strength, both $p \leq 0.05$). However, no significant ($p > 0.05$) changes in frailty score or frailty prevalence were observed in both intervention and control groups. Second, each of the mean cortical regions of interest and regional SUVRs (frontal cortex, lateral temporal cortex, parietal cortex, precuneus/posterior cingulate cortex (PC/PCC), hippocampus, basal ganglia, and global SUVR) was

associated with gait speed, TUG, SPPB, and weakness. The overall conclusions and suggestions are as follows: High-speed resistance exercise training is effective in improving cognitive function and physical performance in older adults with cognitive frailty. Therefore, it is feasible to use high-speed resistance exercise training to effectively reduce the level of frailty and cognitive disability in older adults with cognitive frailty in community and primary care setting. Furthermore, none of the cortical or regional amyloid levels in the brain were associated with each other in the MCI and cognitive frailty groups. Nevertheless, the present study demonstrated the association between brain amyloid- β levels and weakness depending on the SUVR values of all the brain regions. Further, the global SUVR (temporal cortex, parietal cortex, PC/PCC, basal ganglia) was associated with gait parameters. However, the debate is far from closed, and further studies in this field are needed to confirm or refute our findings. Additional research is needed to elucidate the neural mechanisms underlying this association, ideally involving exercise interventions designed to investigate causal relationships.

Keywords: Amyloid imaging, Amyloid beta, Cognitive frailty, Frail elderly, Mild cognitive impairment, Resistance training,

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I . Study Background

As the population of individuals ages 80 and older explodes, the burden of dementia is expected to be one of the most daunting and costly challenges associated with longer life expectancies. Early detection of at-risk older adults and the development of interventions focused on preventing loss in quality of life are increasingly important health measures. Diagnosing dementia, especially in the early stages of the disease is difficult; many cases go undiagnosed even in the intermediate or more advanced stages (National Institute on Aging, 2011). The missed diagnosis is partly attributed to the complexity of the condition that cannot be attributed to a single functional or cognitive domain, and the need to better understand the underlying neuropathology contributing to non-aging related cognitive impairment cannot be overstated (Buchman & Bennett, 2013; Canevelli & Kelaiditi, 2014; Kelaiditi et al., 2013). The relationship between physical frailty and cognitive impairment has become increasingly apparent with recent studies suggesting a close relationship between the two elements. Efforts focused on understanding the relationship may provide a means to identify individuals with cognitive impairment caused by non-neurodegenerative and possibly reversible conditions (Buchman & Bennett, 2013; Kelaiditi et al., 2013). Although, frailty and cognitive impairment have been shown to be related, both constructs have long been studied separately (Kelaiditi et al., 2013). To address this gap, the International Consensus Group organized by the International Academy on Nutrition and Aging (IANA) and the International

Association of Gerontology and Geriatrics (IAGG) convened on April 16th, 2013 in an effort to identify domains of physical frailty and cognition. Additionally, the consensus group recommended formal assessments based on studies that supported findings of an association between progressive physical frailty and cognitive impairment in older adults. The new construct called cognitive frailty (Kelaiditi et al., 2013), extends the physical construct with a formal cognitive assessment and a comprehensive assessment of depressive symptoms.

1. Operational and Theoretical Definitions

Establishing a comprehensive understanding of cognitive frailty underscores the need for a critical review of the consensus on operational definitions and tools used to study frailty and cognitive impairment individually.

1.1 Frailty

The first definition of frailty was proposed in 1988 (Woodhouse, Wynne, Baillie, James, & Rawlins, 1988). Since then, the international community failed to agree on a definition of the term or an assessment tool to measure the condition (Abellan van Kan et al., 2008). The International (IANA) Task Force on Frailty identified 17 cohort-based definitions, using different frailty assessment tools. More recently, Rodríguez-Mañas et al in 2013 developed an operational definition using a

Delphi process, which resulted in a consensus on the value of screening for physical frailty in the following six domains: physical performance, including gait speed and mobility, nutritional status, mental health, and cognition. An operational definition was not recommended due to the need to identify a specific combination of clinical and laboratory biomarkers for diagnosis (Rodriguez-Manas et al., 2013). Even though no consensus regarding an operational definition of frailty is available, the theoretical definition, which is generally agreed upon, describes frailty as a multidimensional geriatric syndrome with increased vulnerability to stressors. Frailty is attributed to diminished capacity of different physiological systems resulting in adverse health outcomes that include falls, disability, hospitalizations, and mortality (Abellan van Kan et al., 2008; Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Panza et al., 2011).

The criteria used to identify frailty often depend on the operational definition. The commonly-known criterion is the “phenotypic” definition developed by the Cardiovascular Health Study (CHS) (Fried et al., 2001; Nguyen, Cumming, & Hilmer, 2015). The CHS phenotype includes decline in lean body mass, strength, endurance, balance, walking performance, and low activity (Fried et al., 2001). It allows for a continuous scoring system versus a nominal system to highlight the multidimensional nature of frailty. The components have concurrent and predictive validity with hazard ratios (HR) ranging from 1.82-4.46 ($p < 0.05$) for outcomes that include incident disease, hospitalization, falls, disability and mortality in community-dwelling older adults (Fried et al., 2001). Additionally, the CHS model has positive predictive

validity (PPV) for the detection of physical limitations. The Edmonton Frail Scale (EFS) has been used to evaluate the social support domain and has been validated by non-specialists with no formal training in geriatric care (Rolfson, Majumdar, Tsuyuki, Tahir, & Rockwood, 2006). The construct validity for detection of physical performance by the EFS was statistically significant ($r = -0.58$, $p = 0.006$, $n=21$) with inter-rater reliability ($k = 0.77$, $p = 0.0001$) and internal consistency (Cronbach $\alpha = 0.62$)¹². However, the use of the EFS was not statistically significant for the detection of cognitive impairment ($r = -0.005$, $p = 0.801$, $n=30$) (Rolfson et al., 2006).

Other validated frailty instruments with unique operational definitions described in the literature include: the Frailty Index (FI), Clinical Frailty Scale, Study of Osteoporotic Fractures (SOF), and SPPB (gait speed, repeated chair stands, and tandem balance tests) validated in the Established Population for Epidemiologic Studies of the Elderly (EPESSE), and Tilburg Frailty Indicator (TFI) encompassing three frailty domains (physical, psychological and social) (Ensrud et al., 2008; Gobbens, van Assen, & Schalk, 2014; Rockwood et al., 1999; Studenski et al., 2003). Several frailty assessment tools are time consuming with slightly different measurement properties, and are not practical except for research purposes. Studies reflect the lack of consensus and ongoing debate on operationalizing the definition for frailty (Pel-Littel, Schuurmans, Emmelot-Vonk, & Verhaar, 2009).

1.2 Cognitive Impairment

The theoretical and operational definition of the progressive loss of memory unrelated to normal aging is not established. Mild cognitive impairment (MCI) was first proposed by Petersen et al in 1999 and revised by the International Working Group on Mild Cognitive Impairment (Winblad et al., 2004). MCI is the most commonly used term to describe a progressive measure of change in memory that differs from healthy aging adults. The recommended criteria for MCI include self- and informant-reported memory impairment or evidence of decline over time involving objective tasks with preserved activities of daily living, and minimal impairment in complex instrumental functions with no diagnosis of dementia (Winblad et al., 2004). As stated in the Diagnostic Statistical Manual-5 (DSM-5), MCI is a neurocognitive disorder varying from mild (mNCD) to major (mNCD) suggesting the heterogeneity of cognitive impairment (Sachs-Ericsson & Blazer, 2015).

The Mini-Mental Status Exam (MMSE) is one of the most commonly used screening tools for the assessment of MCI and dementia in research and clinical settings. The MMSE offers modest accuracy but has the best value for excluding a diagnosis of dementia in community and primary care settings. with sensitivity (85.1%), specificity (85.5%), positive predictive value (34.4%), and negative predictive value (98.5 %) (Mitchell, 2009). Several cognitive screening instruments (CSI) are available, although many of them have not been validated for the detection of early cognitive impairment. Several CSI have been evaluated, specifically the

MMSE, the Six-Item Cognitive Impairment Test (6CIT), the Montreal Cognitive Assessment (MoCA), the Test Your Memory (TYM) test, and the Addenbrooke's Cognitive Examination-Revised (ACE-R) for accuracy in diagnosing dementia and mild cognitive impairment (Larner, 2014). Based on Cohen's effect size, all of the CSI were effective for the detection of dementia; the MoCA (1.45) was most appropriate for the detection of MCI and non-demented conditions with medium ranges for the ACE-R (0.73), MMSE (0.69), 6CIT (0.65), and TYM (0.48) (Larner, 2014).

1.3 Mild cognitive impairment and Cognitive Frailty

A major controversial point regarding the definition of cognitive frailty is reversible cognitive impairment ($CDR = 0.5$), which can be fairly confusing. It was proposed that a CDR value of 0.5 was equivalent to the MCI stage (Hughes et al., 1982; Morris, 1993). On one hand, this criterion makes it difficult to discriminate cognitive frailty from MCI, prodromal period AD and CIND; on the other hand, progressive neuronal cell loss during the MCI stage may surpass the physiological ability of the brain to compensate; thus, irreversible cognitive damage might have already occurred (Gomez-Isla et al., 1996; Aisen, 2008). Based on the neuropsychological profile, MCI is divided into three subtypes: amnesic MCI is considered to progress preferentially to AD; MCI with a slight impairment of multiple cognitive domains may progress to either AD or vascular dementia or be part of the

normal cognitive aging process; and single-domain non-memory MCI may progress to non-AD dementia (Portet et al., 2006). Some MCI patients have symptoms that are reversible and can recover to regain normal cognitive function. The cognitive functions of other patients may even be stable and not change throughout the remainder of their lives. However, more MCI patients exhibit an irreversible, progressive reduction in cognition (Golomb et al., 2004; Matthews et al., 2008; Mitchell and Shiri-Feshki, 2009). In the early stage of cognitive decline, cognitively impaired individuals often display a functional loss in more complicated tasks (e.g., instrumental activities of daily living), whereas the functional loss of simpler tasks (i.e., activities of daily living) appears in the more severe stage of cognitive impairment (Millán-Calenti et al., 2012; Njegovan et al., 2001; Barberger-Gateau et al., 1992). Studies have revealed that 34% of MCI patients experience obstacles in performing the instrumental activities of daily living (e.g., managing the household economy), and this percentage is significantly higher than that (5%) of non-MCI populations (Morris, 2012). According to the definition, the appearance of physical disabilities is clearly not a component of physical frailty. Previous studies indicated that immunotherapy-based clinical trials involving humanized monoclonal antibodies against amyloid β peptide, bapineuzumab and solanezumab, failed. Moreover, in a 5-year comparative study, Ginkgo biloba extract and a placebo were used as agents of intervention to examine a large cohort of subjective cognitive impairment and/or MCI subjects (2854 individuals); the results revealed that Ginkgo biloba extract, a potent antioxidant, could not reduce the risk of progression of impairment in AD patients. A lesson learned from these studies is that the target (cognitive impairment in the study

subjects) of secondary prevention should be a focus in pre-clinical AD or asymptomatic AD (Doody et al., 2014; Vellas et al., 2012, 2013). At the asymptomatic stage, patients have produced in vivo signals (e.g., positive for certain biomarkers) that are indicative of their brain diseases (Sperling et al., 2011, 2013; Caselli and Reiman, 2013).

1.4 Cognitive Frailty

The International Consensus Group (IAAA/IAGG.) report addresses the need to focus research efforts on a clinical condition characterized by physical frailty and cognitive impairment, in the absence of overt dementia or underlying neurological conditions (Kelaiditi et al., 2013). According to the Consensus Group, cognitive frailty is considered a heterogeneous clinical syndrome in older adults with evidence of: 1) physical frailty and cognitive impairment (Clinical Dementia Rating score of 0.5); and 2) exclusion of a clinical diagnosis of Alzheimer's disease or other dementia (Kelaiditi et al., 2013). The International Consensus Group suggested a list of possible biological, clinical, and imaging markers to improve the detection of physical disability and neurodegenerative disease (Buchman & Bennett, 2013; Kelaiditi et al., 2013). The list was not intended to be complete, accurate or exhaustive; instead, the intent was to stimulate research to further characterize a complex multidimensional geriatric syndrome and encourage the development of preventive and therapeutic interventions (Kelaiditi et al., 2013).

Worsening cognitive impairment may increase the risk of frailty, which may be associated with cognitive impairment (Canevelli & Kelaïditi, 2014). The mechanisms and the direct relationship underlying the dynamic association of physical frailty and cognitive impairment presented in the theoretical framework for cognitive frailty remains unexplained. In order to develop a deeper understanding, the psychometric properties for the instruments measuring cognitive frailty must be clearly defined.

2. Physical and cognitive functional declines are linked

2.1 Clinical and subclinical factors shared between frailty and cognitive disorders

Multiple subclinical and clinical conditions appear to mediate the physical and cognitive age-related declines. For example, depression has been related to hippocampal atrophy and subsequent mild cognitive impairment (MCI) (Panza et al., 2010) as well as the development or worsening of the physical frailty syndrome in older persons (Lohman & Mezuk, 2013; Mezuk, Edwards, Lohman, Choi, & Lapane, 2012). Similarly, cardiovascular risk factors (e.g., diabetes, dyslipidemia, hypertension, inflammation, hyperhomocysteinemia) may be responsible for cumulative neurological damage (Jefferson et al., 2011; Jefferson et al., 2010; Kamat, Kamat, & Grossberg, 2010) and are positively associated with frailty (Collerton et al., 2012; Kalyani, Varadhan, Weiss, Fried, & Cappola, 2012; Lu, Lin, & Kuo, 2009; Phan, Alpert, & Fain, 2008). It has also been suggested that genetic mutations (e.g. aPOE4) as well as environmental factors (e.g., low education, unhealthy dietary patterns, low physical and mental activity, smoking, high alcohol consumption) may negatively influence the aging brain (Kamat et al., 2010; Morley, 2010) rendering it more fragile and increasing the risk of developing age-related diseases. Genes underlying apoptotic and transcription regulation such as 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), Caspase 8 (CASP8), CREB-binding protein (CRBBP), lysine acetyltransferase 2b (KAT2B), and beta-transducin repeat containing (BTTRC) loci (Ho et al., 2011), and environmental factors such as nutrition

and physical activity are also strongly related to physical (Dato et al., 2012) and cerebral (Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013) frailty. Additional pathophysiological mechanisms underlying the oxidative damage and functional changes in the hippocampus and prefrontal cortex have been identified as important factors potentially mediating cognitive decline and leading to dementia (Bishop, Lu, & Yankner, 2010). Recently, Clegg et al suggested that structural and functional changes in the aging brain in combination with frailty may identify elderly people at particularly high risk of adverse outcomes (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013).

2.2 Physical and cognitive decline in frailty

The close relationship between physical and cognitive decline in older persons can be directly observed in clinical practice. Recently, Le G rontop le du Centre Hospitalier Universitaire de Toulouse (France) in collaboration with D partement universitaire de m decine g n rale Toulouse (DUMG) and the regional health authority (Agence Regionale de sant  of the Midi Pyr n es region, France) has developed an innovative Platform for the Evaluation of Frailty and the Prevention of Disability, thus integrating frailty into clinical practice. After the first 6 months of operation and evaluation of 160 older adults, data show that more than half of the assessed frail individuals (52.9 %) presented a clinical dementia rating score (CDR) of 0.5, suggesting objective cognitive impairment (Subra et al., 2012). A few of these

patients are likely to present an early undiagnosed phase of neurodegenerative condition, or show a non-dementia-related accelerated decline. It is possible that several other patients may not experience a further cognitive decline (Figure 1). The need for distinguishing different risk profiles for health-related events within a unique theoretical definition of frailty is crucial in order to adopt adequate countermeasures and facilitate the development of personalized interventions. In this context, it is noteworthy that physical impairment is often responsible for increasing sedentary behavior and social isolation in older persons. These two factors not only contribute to a vicious cycle detrimental to physical health, but may also trigger cognitive decline independent of a neurodegenerative condition.

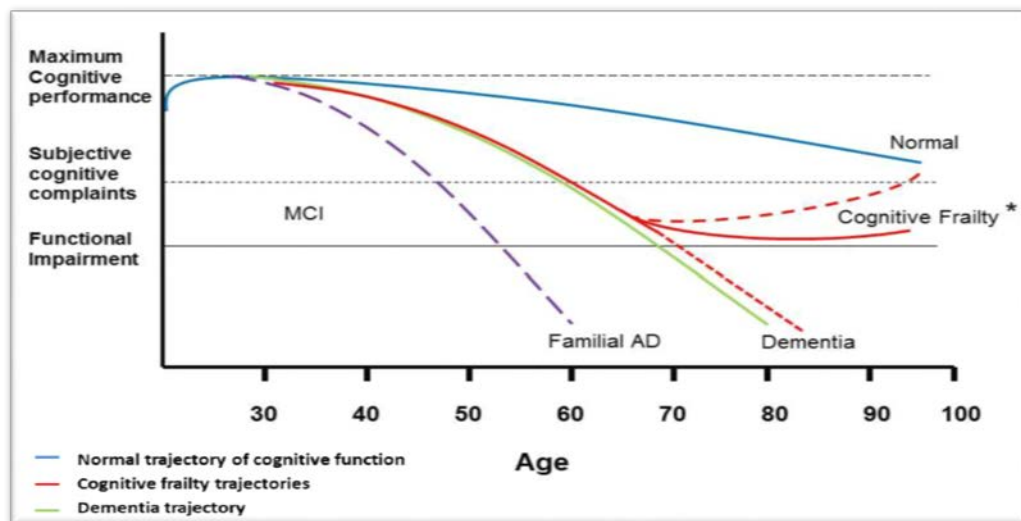


Figure 1. Different trajectories of cognitive function according to specific conditions
 * adapted and modified with permission from authors

2.3 Panel discussion on the definition of Cognitive Frailty in older adults

Older non-demented persons can be operationally categorized into four groups according to their physical and cognitive status. These groups include:

- (i) Robust older individuals (i.e., no evidence of physical frailty) without cognitive problems (i.e., normal brain aging);
- (ii) Physically frail older adults with normal cognitive functioning (as indicated by a clinical dementia rating [CDR] equal to 0), including individuals with subjective memory complaints;
- (iii) Older adults with no physical frailty but already exhibiting cognitive impairment (CDR=0.5); and
- (iv) Older adults with physical frailty and cognitive impairment (CDR=0.5).

The consensus panel was particularly interested in discussing the group (iv), in order to evaluate the relationship between cognitive impairment and physical impairment rather than neurodegenerative disorders, suggesting that cognition is a component of frailty syndrome.

2.4 Proposed definition of cognitive frailty

After evaluating the current literature, the consensus panel defined the so-called “cognitive frailty” as a heterogeneous clinical manifestation characterized by

the simultaneous presence of both physical frailty and cognitive impairment. In particular, the key factors defining such a condition include:

- Presence of physical frailty and cognitive impairment (CDR=0.5);
- Exclusion of concurrent Alzheimer's disease or other dementias.

The two defining criteria imply that cognitive frailty is characterized by reduced cognitive reserve, but is different from physiological brain aging. At the same time, it is noteworthy that under different circumstances, cognitive frailty may also represent a precursor of neurodegenerative processes. Cognitive frailty may be potentially reversible. A psychological component of the condition is evident and increases individual susceptibility to stressors.

The proposed definition addresses a current gap in the existing literature, as it particularly allows the conceptualization of cognitive impairment based on the individual physical domain and not based on concomitant neurological disease (Figure 1). In other words, this approach represents the first attempt to identify a clinical entity including both physical and cognitive dimensions. In fact, dementia and disability are complex conditions that should not be attributed to a single domain. The identification of cognitive frailty in older persons may facilitate the design of preventive and/or rehabilitative interventions, under specific clinical settings. Alzheimer's disease is the most common type of neurodegenerative disorder. However, it is not the aim of the consensus group to study neurodegenerative disorders although frailty is characterized by cognitive impairment due to physical

conditions. As a further clarification, the frailty syndrome, although phenotypically driven by the physical domain, is a systemic condition. The term “cognitive frailty”, according to the consensus, is a condition of cognitive impairment caused by physical conditions.

3. Potential preventive interventions

Including cognition in the definition of frailty and exploring the different health trajectories that a frail person with subjective cognitive impairment will follow may lead to potential preventive interventions. Research in this direction will further inform public health policies to implement evidence-based research findings for preventive efforts and clinical trials. Initially, a list of preventive interventions may be considered that include promotion of physical activity, cognitive stimulation and training, healthy dietary habits (e.g., Mediterranean diet), smoking cessation, promotion of emotional resilience, active and socially integrated lifestyles, optimal daily sleep, maintenance of optimal body weight, and metabolic control (including control of dyslipidemia, diabetes and blood pressure) (Desai, Grossberg, & Chibnall, 2010). As a further step, the causes of frailty need to be identified to enable the implementation of multidomain interventions based on evidence-based research and personalized needs. Evaluation of pharmacological therapy and drug use are also recommended. Multidomain interventions might prove useful if focused on the physical, nutritional, cognitive and psychological domains in order to improve the well-being and quality of life in the elderly. The promotion of physical exercise, correction of nutrient deficiencies, potential nutrient supplementation, and implementation of cognitive and psychological training may contribute comprehensively to the well-being and quality of daily life in older persons. These strategies may be ineffective if focused on single components and fail to capture the complexity of the phenomenon.

II . Experimental Researches

In the present dissertation, two study of experimental were investigated. The first intervention study is to determine the effect of high-speed resistance exercise training on cognitive function and physical performance in older adults with cognitive frailty. Second study, examine the association between brain amyloid- β accumulation as assessed by a brain imaging biomarker and Physical frailty (weight loss, weakness, exhaustion, slowness, low physical activity) in older Adults with mild cognitive impairment (MCI) and cognitive frailty. To achieve our objective, patients with cognitive frailty were included in this controlled trial study on the basis of the following: 1) CDR of 0.5 with the absence of concurrent dementia; 2) At least one CHS criterion of physical frailty (inclusion frailty and pre-frailty); and 3) Ability to walk 10-m without requiring a walking aid.

1. Study I .

Effects of Resistance Exercise Training on Cognitive Function and Physical Performance in Cognitive Frailty: A Randomized Controlled Trial

2. Study II .

Physical Frailty and Amyloid- β Brain Imaging Biomarker in Older Adults with Cognitive Frailty

STUDY 1

Effects of Resistance Exercise Training on Cognitive
Function and Physical Performance in Cognitive Frailty: A
Randomized Controlled Trial

Abstract

Background: Cognitive frailty is defined as the presence of both physical frailty and cognitive impairment (clinical dementia rating score = 0.5), in the absence of dementia. It is characterized by concurrent physical frailty and potentially reversible cognitive impairment. In this study, we sought to elucidate the effects of high-speed resistance exercise training on cognitive function and physical performance in older adults with cognitive frailty.

Methods: We conducted a parallel-group, randomized controlled trial involving community-living older adults with cognitive frailty. The participants' mean age was 73.9 (\pm 4.3 SD) years, and 69.8% (n=30) were female. Two different 4-month interventions included high-speed resistance exercise training group (n=22) and a control group (balance and band stretching, n=23). Frailty score and prevalence, cognitive function (memory, processing speed, cognitive flexibility, working memory, executive function), physical function (SPPB, TUG, gait speed), and muscle strength (grip strength, knee extension strength) were assessed at baseline, 8 weeks, and 16 weeks.

Results: Statistical analysis showed that exercise improved performance significantly in the tests for cognitive function (processing speed and executive function, both $p < 0.05$), physical function (SPPB, TUG, gait speed, both $p < 0.05$), and muscle strength (grip strength, knee extension strength, both $p < 0.05$).

Conclusion: In conclusion, our findings indicate that high-speed resistance exercise

training approaches are effective in improving cognitive function and physical performance in older adults with cognitive frailty. This study shows that it is feasible to identify older adults with cognitive frailty in the community and primary care setting for effective intervention to reduce their level of frailty and cognitive impairment.

Keywords: cognitive frailty, cognitive impairment, disability, physical frailty, resistance training,

1. Introduction

Frailty is an age-related, biological syndrome characterized by decreased biological reserves, due to dysregulation of several physiological systems. It increases the individual risk for stress-induced impairment, and is associated with poor outcomes (i.e., hospitalization, institutionalization, fall, functional disability, and disability) (Feng et al., 2017; Tarazona-Santabalbina et al., 2016). A widely used clinical research definition of the frailty syndrome in the Cardiovascular Health Study (CHS) frailty phenotype, consists of a combination of shrinking (unintentional weight loss), weakness (indicated by muscle strength), poor endurance and energy (per self-reported exhaustion), slowness (demonstrated by slow walking speed), and low physical activity (Fried et al., 2001). According to the current consensus, physical frailty is potentially reversible with appropriate intervention (Ng et al., 2015). Accordingly, early detection of at-risk older adults and the development of interventions focused on preventing loss in quality of life play an increasingly important role (Sargent & Brown, 2017).

The relationship between physical frailty and cognitive impairment has become increasingly apparent with recent studies suggesting an interrelationship (Ruan et al., 2015; Sargent & Brown, 2017). Physical and cognitive impairment frequently overlap in older adults, however, cognition is not included in the physical frailty phenotype (Montero-Odasso et al., 2016). It has been consistently shown that physical frailty is associated with cognitive impairment and dementia (Robertson, Savva, Coen, & Kenny, 2014). Although frailty and cognitive impairment have been

shown to be related, both constructs have long been studied separately (Sargent & Brown, 2017). To address this gap, the international consensus group comprised of investigators from the International Academy of Nutrition and Aging (IANA and the International Association of Gerontology and Geriatrics (IAGG recently convened in Toulouse, France to establish a definition of cognitive frailty in older adults (Kelaiditi et al., 2013). Additionally, the consensus group recommended formal assessments based on studies that supported findings correlating progressive physical frailty with cognitive impairment in older adults. The new construct called cognitive frailty, defined as the presence of both physical frailty and cognitive impairment (Clinical dementia rating score (CDR) = 0.5), in the absence of dementia, is characterized by concurrent physical frailty and potentially reversible cognitive impairment (Kelaiditi et al., 2013). The underlying rationale suggests that the cognitive impairment in these patients is primarily due to physical deterioration rather than neurodegenerative processes (Montero-Odasso et al., 2016).

Several meta-analyses and randomized controlled trials have reported that physical activity is associated with improvements in attention, processing speed, and executive function (P. J. Smith et al., 2010) as well as sensorimotor ability in older adults. Indeed, aerobic exercise may lead to an increase in brain volume (Shimada et al., 2017) and enhance functional connectivity between parts of the frontal, posterior, and temporal cortices (Voss et al., 2010) in non-frail older adults. However, few studies have examined the effect of other types of exercises on cognitive function. For example, it has been observed that resistance training contributes positively and

significantly to the improvement of brain functional plasticity, executive function and response inhibition (Liu-Ambrose et al., 2010; Yoon et al., 2017). However, currently no specific exercise interventions can be totally recommended for brain function and physical health promotion in older adults with cognitive frailty as the evidence base is small and of limited quality. Also, current evidence is limited, and studies are needed to determine the role of exercise parameters (e.g. volume, types, and intensity) in cognitive function (Dulac & Aubertin-Leheudre, 2016).

Consequently, in this study, we sought to elucidate the effects of high-speed resistance exercise on cognitive function and physical performance in older adults with cognitive frailty. We hypothesized that low-intensity high-speed resistance exercise training may be effective in improving physical functions; muscle strength and cognitive function. We used a randomized control trial design to measure cognition and physical performance before and after, and high-speed resistance training intervention.

2. Methods

2.1 Study sample

We selected 65 participants who were 65 years and older, lived in Seoul, Korea, and had no history of depression; chronic disease; degenerative neurologic disease; hospital admission in the past 12 months for any reason; not illiterate; had no stroke or other cardiopulmonary disease; or dementia. Additional inclusion criteria included the ability to walk 10 m without a walking aid, a CDR of 0.5, and pre-frail and frail older adults, as of August 2016. Thus, the remaining 65 subjects were eligible to participate in this study. Prefrail and frail older adults were identified based on five Cardiovascular Health Study (CHS) criteria defining physical frailty (Kelaïditi et al., 2013): unintentional weight loss, slowness, weakness, exhaustion, and low activity, which were scored 1 if present and 0 if absent. The total cumulative scores ranging from 0 to 5 were used to classify a participant as robust (score = 0), prefrail (score = 1 to 2), or frail (score = 3 to 5). Cognitive frailty was defined as the simultaneous presence of physical frailty, as described above, with cognitive impairment, defined as a CDR of 0.5, and absence of concurrent dementia (Kelaïditi et al., 2013). The participants were randomly assigned to one of the two groups: high-speed resistance exercise training group (n=32) and control group (balance and resistance band stretching, n=33). At the end of the 16-week study, 45 participants including 22 from the exercise group and 23 from the control group remained. The study protocol was approved by the Institutional Review Board of SNUBH (BRMH IRB No. 16-2016-26)

2.2 Measurements

Diagnosis frailty phenotype

Frailty was measured according to the CHS criteria (Fried et al., 2001) involving five components operationally defined as:

- 1) Unintentional weight loss: body mass index (BMI: weight/height^2) < 18.5 kg/m² or self-reported unintentional weight loss of 4.5 kg in the last one year.
- 2) Slowness was assessed using 4-meter fast gait speed test. Participants were timed in seconds while walking 4 meters and an average of 2 measurements was obtained. A speed < 0.8 m/s indicated frailty-related slowness.
- 3) Weakness was defined as low grip strength in each individual corresponding to gender and body mass index (BMI). Grip strength was measured using a hand-to-hand dynamometer (Takei Scientific Instruments, Niigata, Japan). Each participant stood and gripped the hand-to-hand dynamometer handle. Upon verbal command, the handle was gripped as strongly as possible. It was repeated four times with a break in between. The average grip strength in kilograms was recorded.
- 4) Exhaustion included self-reported exhaustion, identified by two questions from the Center for Epidemiologic Studies Depression Scale (CES–D) scale. “How often have you ever felt that everything you had done was useless in the last week?” and “How often have you ever felt that everything you had to do was not in a mood to do during the last week?” Exhaustion was indicated

by responses of “most of the time” and “often”

- 5) Low physical activity corresponded to responses to International Physical Activity Questionnaire (IPAQ) items concerning low, middle, and high levels of physical activity. Responses describing low physical activity were indicative of frailty.

2.3 Physical function and muscle strength

Short physical performance battery (SPPB) was used to assess gait speed, chair stand, and balance tests. It has been used as a predictive tool for possible disability and facilitated the monitoring of function in older people. Each test received a performance score, with scores ranging from 0 points (worst performance) to 12 points (best performance). The tests comprised the chair stand test (four points), balance test (four points), and 4-m gait speed test (four points) (Guralnik et al., 2000). The Timed Up and Go test (TUG) is a simple test used to assess a person's mobility and requires both static and dynamic balance. TUG was defined as the time from the moment the buzzer sounded to the moment the subject sat back down on the chair, detected automatically using a piezo resistive pressure sensor located under the seat. The subject rises from the chair, walks 3 m in a linear path, performs a 180° turn, walks back to the chair, and sits down (Sasaki, Senda, Nishida, & Ota, 2010). In the gait speed test, the 4.44-m gait test was used. Three lines were drawn horizontally in the measuring area. The interval between the first and second lines was 1 m, and 4.44 m between the second and third lines, for a total of 5.44 m. Each participant stood on

the first line and walked to third line immediately upon verbal command. The average duration of the two trials of walking speed test was recorded.

Lower limb concentric dynamic strength was measured using a HUMAC NORM isokinetic dynamometer (CSMi Solutions, Stoughton MA, USA). The knee extension peak torques of dominant lower limb were evaluated for the isokinetic contraction test. The subjects performed a maximal test of 3-time and 5-time repetitions. Each maximal strength test was conducted at an angular speed of 60°/s for isokinetic muscle strength and an angular speed of 180°/s for isokinetic muscle power measurement (Power, Dalton, Rice, & Vandervoort, 2011). The exercise was performed twice prior to testing in order to obtain optimal results by allowing the subjects to familiarize themselves with the test.

2.4 Assessment of cognitive function

To assess participants' cognitive function, a sensitive and validated neuropsychological test battery was used. The Korean version of Mini-Mental State Examination (MMSE-K) (Jeong, Cho, & Kim, 2004), CDR scales, and the neuropsychological battery including the Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K), were used for all participants by a single rater. MMSE-K is commonly utilized to screen for dementia. The test consisted of 11 questions and tasks with a total of five cognitive domains: orientation (10 points), memory (6 points), attention (5 points), language ability (7

points), and comprehensive/judgment (2 points). The highest possible score was 30, with higher score indicating higher level of cognitive function. CERAD-K is a paper and pencil-based memory test battery developed in Korea. Its reliability and validity have been verified. It is widely used in clinical practice. This neuropsychological test assessed the following: an executive domain in the category of verbal fluency test (0 – 24 point), a language domain of Modified Boston Naming Test (BNT) (0 – 15 point), a memory domain of Word-List-Learning test (0 – 30 point) with delayed recall (0 – 10 point) and recognition (0- 10 point), and a visuospatial domain of visual construction test (0 – 11 point). The total score of the CERAD-K was calculated by summing scores of the six subtests (Shin et al., 2008). CDR was calculated as the sum of all six items (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) in CDR scale. Composite rating consisted of five levels: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe) (Park et al., 2014).

The cognitive function was assessed using 4 cognitive tasks: 1) Rey 15-Item memory test, 2) Trail Making A&B Test, 3) Digit Span (both forward and backward) test, and 4) Frontal assessment battery (FAB)

- Memory: Recall and recognition were assessed using the Rey 15-Item memory test (Boone, Salazar, Lu, Warner-Chacon, & Razani, 2002). The test involves memorization of 15 different items (letters, numbers, and simple geometric shapes) presented in five rows (three items/row). Each participant was shown a paper with 15 different items for 10 s. The paper was removed

and the participant recorded in writing as many items as possible, based on recall. The recognition task scores used two parts.

- Processing speed and cognitive flexibility: Processing speed and cognitive flexibility were assessed using the Trail Making A&B Test (Bowie & Harvey, 2006). The trail making test consists of two parts. In Part A (TMT-A), the subject was tasked with listing numbers 1-25 in ascending order (Bowie & Harvey, 2006). In Part B (TMT-B), the subject drew numbers and letters in alternating order. The maximum amount of time to complete Part B was 300 s. TMT-B is more difficult than TMT-A because of the increased demand for motor speed and visual search (Gaudino, Geisler, & Squires, 1995).
- Working memory: The Digit Span test was used. Respondents were asked to recall numbers forward (range 3-9) and backward (range 2-8) (Korten et al., 2014).
- Executive functions: The patients underwent a global screening of executive functions using the Korean version of the FAB (Kim et al., 2010), which consisted of six subset test items including conceptualisation (abstract reasoning), item flexibility (verbal fluency), motor programming (organization, maintenance and execution of successive actions), sensitivity to interference (conflicting instructions), inhibitory control (inhibit inappropriate responses), and environmental autonomy (prehension behavior). The administration time of the FAB is about 10 min.

Based on these four cognitive tasks, five cognitive domain scores were created as a mean of factor analyses. A higher score in 3 domains and a lower score in 2 domains

suggested better cognitive function.

2.5 Resistance exercise intervention

A high-speed resistance training program is defined as a contraction phase expected to be accomplished as quickly as possible, a 1-s pause, and an eccentric contraction exceeding 2 s (Sayers & Gibson, 2014). Independent exercise lasting 1h was conducted 3 times each week for 16 weeks. High-speed resistance exercise regimens were based on the use of elastic exercise bands, based on previous intervention (Yoon et al., 2017). Each session included a 10-min warm-up, 40-min high-speed resistance training (seated row, one leg press, applied pec deck flus, seated leg raise, lateral raise, semi squats, wide squats, bridging), and 10 min of cooling down. The sessions were separated by a minimum of 48 h and were performed under the direct supervision of an exercise instructor to ensure safety and adherence with the exercise protocol. Exercise intensities were set by the color of the elastic exercise band. In the high-speed resistance training group, blue elastic bands (tension: low, 20 Nm) were used and the participants were instructed to perform exercise training at a perceived exertion rate of 12-13 (“Somewhat hard”). The high-speed resistance exercise consisted of 2-3 sets of 12-15 repetitions. Participants in the control group were asked to continue their routine daily activities and performed static and dynamic stretching (using elastic exercise band) twice weekly for 1 h, over 16 weeks. Our exercise program followed the guidelines for older adults recommended by the

American College of Sports Medicine.

3. Statistical analyses

Statistical analyses were performed using SPSS 22.0 (IBM Corporation, Chicago, IL). Categorical variables were expressed as percentages and continuous variables with mean and SD. Intervention and control group older patients were compared using the χ^2 test (categorical variables) and Student's t-test (continuous variables). The training-related effects were assessed using a two-way ANOVA with repeated measures (group x time). Tukey's post hoc procedures were performed to locate the pairwise differences between the mean values. A p-value < .05 denoted statistical significance. The magnitudes of effect size were 0.20, 0.60, and 1.2 for small, moderate and large effects, respectively (Hopkins, Marshall, Batterham, & Hanin, 2009).

4. Results

4.1 Baseline Characteristics

We screened 66 potential participants. All the 65 were eligible and were randomized (33 to high-speed resistance exercise training and 33 to the control group). The participants' mean age was 73.9 (\pm 4.3 SD) years, and 69.8% (n=30) were female. Frailty symptoms included predominantly weakness (49%) and slowness (35%), low physical activities (26%), exhaustion (21%), and 9% shrinking. No significant differences ($p > 0.05$) were observed among the groups in descriptive and dependent variables at baseline. (Table 1).

Table 1. General characteristics of subjects

	Total N=43	Intervention Group, N= 20	Control Group, N= 23	P- value
Demographics				
Age, mean (SD)	73.94 \pm 4.27	73.82 \pm 4.37	74.03 \pm 4.27	.860
Female, n (%)	30 (69.8%)	14 (70.0%)	16 (69.6%)	.848
Education, y, mean (SD)	9.08 \pm 4.13	8.09 \pm 3.50	9.77 \pm 4.44	.145
MMSE, mean (SD)	24.22 \pm 2.31	24.23 \pm 2.89	24.22 \pm 1.86	.990
BMI (kg/m ²)	24.57 \pm 3.06	24.86 \pm 2.73	24.38 \pm 3.30	.569
BMD (g/m ²)	1.11 \pm 0.19	1.14 \pm 0.18	1.10 \pm 0.19	.468
Frailty criteria, n (%)				
Mean (SD) score, (range: 0-5)	1.49 \pm 0.74	1.63 \pm 0.90	1.37 \pm 0.56	.237
Slow gait speed	15 (35%)	8 (40%)	7 (30%)	.531
Shrinking	4 (9%)	2 (10%)	2 (9%)	.702
Weakness	21 (49%)	11 (55%)	10 (43%)	.371
Exhaustion	9 (21%)	2 (10%)	7 (30%)	.519
Low activity level	11 (26%)	6 (30%)	5 (22%)	.443
CERAD-K, Total score				
Verbal fluency (score)	14.26 \pm 4.69	14.00 \pm 4.69	14.44 \pm 4.76	.740
Boston Naming Test (score)	10.07 \pm 2.29	9.18 \pm 2.42	10.69 \pm 2.01	.016
Word-List-Learning test (score)	13.43 \pm 3.32	13.32 \pm 3.55	13.50 \pm 3.20	.845
Delayed recall (score)	4.93 \pm 1.65	4.91 \pm 1.82	8.82 \pm 1.05	.951
Recognition (score)	8.69 \pm 1.43	8.82 \pm 1.05	8.59 \pm 1.64	.575
Visual construction test (score)	8.13 \pm 1.76	9.27 \pm 1.67	9.03 \pm 1.84	.625

Abbreviations: BMI, body mass index; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Values are presented as mean \pm SD. ANOVA indicates two way repeated ANOVA measures between group and time.

*p<0.05 compared pre with post training,

**p<0.01 compared pre with post training, and

***p<0.001 compared pre with post training.

4.2 Training effects for the Physical frailty variables between groups

During the pre- to post-training period, no significant changes (time x group interaction; $p > 0.05$) in frailty score were observed between the intervention and control groups. Similarly, no significant changes (time x group interaction; $p > 0.05$) in frailty prevalence were observed between the intervention and control groups (Table 2).

Table 2. Training effects (with 90% confidence limits) for the cognitive function variables between groups.

	Baseline	8 weeks	16 weeks	p-value	Effect size
	Mean ± SD	Mean ± SD	Mean ± SD		(Cohen's d)
Frailty score					
Intervention	1.55 ± 0.89	0.70 ± 0.73	0.65 ± 0.93	0.683	0.99 ^{##}
Control	1.48 ± 0.67	0.83 ± 0.72	0.70 ± 0.76		1.09 ^{##}
Frailty prevalence, (%)					
Intervention	1.15 ± 0.37	0.55 ± 0.51	0.45 ± 0.60	0.190	1.40 ^{###}
Control	1.09 ± 0.29	0.78 ± 0.42	0.61 ± 0.50		1.17 ^{##}

Values are presented as mean \pm SD. ANOVA indicates two way repeated ANOVA measures between group and time.

Small

Moderate

Large

4.3 Training effects for the cognitive function variables between groups

Table 3 summarizes the changes in cognitive function from baseline to follow-up at 8 and 16 weeks in the intervention and control groups. There was a significant decrease in processing speed over 16 weeks across intervention group, and significant group x time interaction ($p = 0.036$). At 8 and 16 weeks, intervention showed significant differences compared with control at the post hoc significance level of $p < 0.05$, $p < 0.01$, and 0.21 ES, respectively. Similarly, executive functions increased significantly over the 16 weeks across intervention group, and significant group x time interaction ($p = 0.022$). At 16 weeks, intervention showed significant differences compared with control at the post hoc significance level of $P < 0.05$, 0.74 ES. However, no significant changes (time x group interaction; $p > 0.05$) in memory, cognitive flexibility, or working memory were observed between intervention and either control group (Table 3).

Table 3. Training effects (with 90% confidence limits) for the cognitive function variables between groups.

	Baseline Mean ± SD	8 weeks Mean ± SD	16 weeks Mean ± SD	p-value	Effect size (Cohen's d)
Memory (score) :rey-15					
Intervention	8.55 ± 2.39	9.85 ± 3.22	10.00 ± 3.71	0.445	0.46 [#]
Control	10.26 ± 2.85	10.96 ± 2.57	10.52 ± 2.79		0.09
Processing speed (sec) : TMT-A					
Intervention	54.15 ± 28.43	50.86 ± 27.07*	48.26 ± 27.33**	0.036	0.21 [#]
Control	43.04 ± 11.95	43.07 ± 16.67	42.59 ± 15.92		0.03
Cognitive flexibility (sec) : TMT-B					
Intervention	163.37 ± 62.45	149.34 ± 46.81	140.82 ± 34.65	0.532	0.45 [#]
Control	188.92 ± 81.38	176.55 ± 62.16	187.20 ± 70.14		0.02
Working memory (score) : Dig F/B					
Intervention	10.20 ± 1.54	10.15 ± 1.42	10.70 ± 1.34	0.448	0.35 [#]
Control	10.09 ± 2.04	10.52 ± 2.11	10.39 ± 1.83		0.14
Frontal Assessment Battery (FAB), (score)					
Intervention	12.00 ± 2.45	12.65 ± 1.95	13.70 ± 2.11*	0.022	0.74 ^{##}
Control	11.87 ± 2.12	12.43 ± 1.78	12.09 ± 2.00		0.11

Values are presented as mean \pm SD. ANOVA indicates two way repeated ANOVA measures between group and time.

*p<0.05 compared to baseline,

**p<0.01 compared to baseline

Small

Moderate

Large

4.4 Training effects for the physical function variables between groups

The results of physical function domain of SPPB, TUG, and gait speed are shown in Table 4. In SPPB, the intervention group showed significant (group x time interaction; $p = 0.001$) increases over 16 weeks. At 8 and 16 weeks, intervention showed significant time effect at the post hoc level of $p < 0.05$, 0.81 ES, respectively. After 16 weeks of intervention, the TUG showed significant group x time interaction ($p = 0.000$). At 8 and 16 weeks, intervention showed significant impact of time at the post hoc significance level of $p < 0.01$, 0.65 ES, respectively. In terms of gait speed, the intervention group showed significant (group x time interaction; $p = 0.027$) increases over 16 weeks. At 8 and 16 weeks, intervention led to significant time effect at the post hoc level of $p < 0.01$, 0.94 ES, respectively (Table 4).

Table 4. Training effects (with 90% confidence limits) for the physical function variables between groups.

	Baseline	8 weeks	16 weeks	p-	Effect size
	Mean \pm SD	Mean \pm SD	Mean \pm SD	value	(Cohen's <i>d</i>)
SPPB (score)					
Intervention	9.25 \pm 2.31	11.00 \pm 1.45*	10.85 \pm 1.60*	0.001	0.81 ^{##}
Control	10.04 \pm 1.46	10.35 \pm 1.19	10.91 \pm 1.20		0.65 ^{##}
TUG (sec)					
Intervention	10.66 \pm 2.41	8.82 \pm 1.82**	9.26 \pm 2.03**	0.000	0.65 ^{##}
Control	9.95 \pm 1.51	9.61 \pm 1.31	9.89 \pm 1.59		0.04
Gait Speed (sec)					
Intervention	6.21 \pm 1.04	5.44 \pm 1.03**	5.34 \pm 0.81**	0.027	0.93 ^{##}
Control	6.04 \pm 0.82	5.90 \pm 0.72	5.58 \pm 0.81		0.56 [#]

Values are presented as mean \pm SD. ANOVA indicates two way repeated ANOVA measures between group and time.

*p<0.05 compared to baseline,

**p<0.01 compared to baseline

Small

Moderate

Large

4.5 Training effects for the muscle strength variables between groups

During the pre- to post-intervention period, relative to muscle strength, the intervention group showed a clinically significant (group x time interaction; $p < 0.05$) increase in grip strength ($p=0.020$, 0.30 ES), isokinetic $60^\circ/\text{sec}$ peak torque ($p=0.004$, 0.19 ES), and isokinetic $180^\circ/\text{sec}$ average power per rap ($p = 0.001$ 0.32 ES). Significant group x time interactions were noted for all measures ($p < 0.05$), with the intervention group resulting in significantly greater improvements in all strength parameters compared with the control group. At 8 and 16 weeks, intervention showed significant time effect at the post hoc level of $p < 0.05$ (table 5).

Table 5. Training effects (with 90% confidence limits) for the muscle strength variables between groups.

	Baseline Mean \pm SD	8 weeks Mean \pm SD	16 weeks Mean \pm SD	p- value	Effect size (Cohen's d)
Grip Strength (kg)					
Intervention	21.41 \pm 6.58	25.02 \pm 7.71*	23.60 \pm 7.76*	0.020	0.30 [#]
Control	21.81 \pm 6.31	23.49 \pm 5.62	23.78 \pm 7.14		0.29 [#]
Isokinetic 60°/sec peak torque / BW					
Intervention	65.05 \pm 25.82	68.85 \pm 37.12*	71.20 \pm 36.68*	0.004	0.19
Control	70.77 \pm 24.32	67.36 \pm 22.45	64.23 \pm 20.72		0.01
Isokinetic 180°/sec average power per rap (watt)					
Intervention	68.32 \pm 40.60	79.77 \pm 45.58*	82.09 \pm 44.63*	0.001	0.32 [#]
Control	72.77 \pm 23.82	68.64 \pm 22.69	66.59 \pm 23.67		0.26 [#]

Values are presented as mean \pm SD. ANOVA indicates two way repeated ANOVA measures between group and time.

*p<0.05 compared to baseline,

**p<0.01 compared to baseline

Small

Moderate

Large

5. Discussion

The aim of the present study was to determine the effect of high-speed resistance exercise training on cognitive function and physical performance in older adults diagnosed with cognitive frailty. To our knowledge, this is the first intervention trial that evaluated the effects of resistance exercise intervention in reversing cognitive frailty. The study provided an opportunity to delineate the cognitive functions and frailty in a controlled trial of subjects with well-defined cognitive and physical performance. To achieve this objective, cognitive frailty was incorporated from the controlled trial study based on the following: 1) CDR of 0.5, and absence of concurrent dementia; 2) at least one CHS criterion of physical frailty (inclusion frailty and pre-frailty); and 3) 10-m walk without a walking aid.

The low-intensity high-speed resistance exercise training had no significant effect in reducing frailty score and prevalence. Frailty is possibly reversible or modifiable by interventions. Previous studies investigating nonpharmacological interventions such as physical exercise showed promising effects on frailty status, functional, and cognitive outcomes (Gine-Garriga, Roque-Figuls, Coll-Planas, Sitja-Rabert, & Salva, 2014; Ruan et al., 2015; Tarazona-Santabalbina et al., 2016). Exercise interventions should be provided for elderly subjects with physical frailty syndromes that are reversible to prevent a reduction in physical functions (Abellan van Kan et al., 2008; Ruan et al., 2015). However, in a few studies, clinical trials failed to show convincing evidence of effectiveness (Rodriguez-Manas & Fried, 2015; Tarazona-Santabalbina et al., 2016), whereas in others exercise partially improved

functional outcomes in the frail population, such as sit-to stand performance, balance, agility, and ambulation, and the level of physical activity (Gine-Garriga et al., 2014; Pahor et al., 2014). Furthermore, previous studies reported that the benefit of multi-domain interventions (nutritional supplementation, psychological treatment, social activities, and physical exercise; respectively) was not evident at 4-month follow-up and was apparent only at 12 months (given that there was no assessment at 6 months) (Cameron et al., 2013). The lack of consistency among the studies is due to the differences in the definition of frailty, training protocols, intervention duration, characteristics of the control groups, and the main outcomes assessed. Thus, a definitive conclusion has yet to be established (Gine-Garriga et al., 2014).

High-speed resistance training significantly improved processing speed and executive function over the course of 16 weeks. Evidence strongly indicates that regular physical exercise leads to positive changes in human biology and psychology, and may prevent the loss of cognitive function (Iuliano et al., 2015). It has been previously reported that exercise improves mood, cognitive function, and quality of life in frail older adults (Langlois et al., 2013). No significant differences were found in other tests following exercise intervention, thus corroborating the findings of several studies suggesting that combination training was more efficient in improving cognitive function in older adults than aerobic or resistance training alone (Dulac & Aubertin-Leheudre, 2016). However, current evidence is limited, and research is needed on the role of exercise parameters (e.g. volume, types, and intensity) on specific cognitive functions. Indeed, it has been reported that the volume, intensity

and variation of physical activities as well as the history of practice were positively associated with processing speed, memory, mental flexibility, executive function and overall cognitive function (Voelcker-Rehage & Niemann, 2013).

A significant improvement was found in SPPB, TUG, and gait speed following high-speed resistance exercise, compared with the control group after 16 weeks. These results reinforce those reported in the LIFE study in which exercise intervention reduced the incidence of major mobility disability (Fairhall et al., 2014; Tarazona-Santabalbina et al., 2016). Our results support a recent study showing an improvement in physical function after completion of high-speed resistance exercise and physical exercise intervention (Cesari et al., 2015; Yoon et al., 2017). Previous studies have highlighted the importance of adherence to exercise programs to improve the scores in functional scales as well as in gait speed (Tarazona-Santabalbina et al., 2016). Multicomponent training programs conducted over 5 months or longer (K. Smith, Winegard, Hicks, & McCartney, 2003) and performed 3 days per week for 30 to 45 min each session contribute to better outcomes.

Our high-speed resistance exercise training program resulted in significant grip strength and knee extension peak torques in the isokinetic contraction test of dominant lower limb. Recent studies show a strong link between cognition and muscle strength (Arts et al., 2016). In addition, muscle strength is an important component of the physical phenotype. Furthermore, maximal strength is a useful predictor of all-cause mortality and old age disability. Maximal strength (especially handgrip strength) is relatively easy to complete and therefore, the variable can be

used as a convenient prognostic tool in the elderly population. This study intervention used resistance exercise training, and the observed improvements in muscle strength (upper and lower body muscle strength) are consistent with those reported elsewhere.

Our study was limited by the small sample size and relatively shorter period of exercise intervention. Therefore, a randomized controlled trial with a larger sample size may provide a deeper insight into the effects of resistance exercise on cognitive function and physical performance. As a further step, the causes of frailty need to be identified to enable the implementation of evidence-based multidomain interventions depending on personalized needs. Evaluation of pharmacological therapy and use of protein and vitamin supplementation is also recommended. Multi-domain interventions might prove useful if focused on the physical exercise, nutritional, cognitive and psychological domains in order to improve the well-being and quality of life in the elderly (Kelaiditi et al., 2013). These strategies may be ineffective if focused on single components and, fail to capture the complexity of the phenomenon. Finally, the pathophysiological mechanisms of cognitive frailty are currently unknown. Therefore, ancillary neuroimaging or brain imaging studies of longitudinal exercise intervention may provide an opportunity to better understand the relation between cognitive frailty and cerebral atrophy, white matter hyperintensities, and amyloid deposits in the brain.

In conclusion, our findings indicate that high-speed resistance exercise training approaches are effective in improving cognitive function and physical performance in older adults with cognitive frailty. This study shows that identifying

older adults with cognitive frailty in the community and primary care setting for targeted intervention effectively reduces their level of frailty and cognitive impairment.

STUDY 2

Physical Frailty and Amyloid- β Brain Imaging Biomarker
in Older Adults with Cognitive Frailty

Abstract

Background: Cognitive frailty and impairment is correlated phenotypically and pathophysiologically with physical frailty. We examined the association between the accumulation of amyloid- β in the brain as a brain imaging biomarker, and phenotype of physical frailty (weight loss, weakness, exhaustion, slowness, low physical activity) in older adults with mild cognitive impairment (MCI) and cognitive frailty.

Methods: The cross-sectional associations between brain amyloid- β as measured with ^{11}C -PIB PET and physical frailty were examined in 48 elderly participants (mean aged 75.1 ± 6.6 years; 73% females). The cortical and regional standard uptake value ratios (SUVRs) were obtained. The main outcome measures included frailty phenotype and physical function: gait speed, short physical performance battery, and timed up and go tests.

Results: Any of the mean cortical regions of interest and each of the regional SUVRs (frontal cortex, lateral temporal cortex, parietal cortex, precuneus/posterior cingulate cortex (PC/PCC), hippocampus, basal ganglia, and global SUVR) was associated with gait speed, TUG, SPPB, and weakness.

Conclusion: The SUVR values of all the brain regions revealed an association between brain amyloid- β and weakness. Further, we found that the global SUVR (temporal cortex, parietal cortex, PC/PCC, basal ganglia) were associated with gait parameters.

Keywords: cognition, cognitive frailty, frail elderly, mild cognitive impairment,

physical function

1. Introduction

Frailty is a pathological aging process that is reversible and occurs at a stage intermediate between age-related diseases and poor prognosis (Ruan et al., 2015). Typically, physical frailty is defined by the presence of at least three of the five following criteria: fatigue, poor muscle strength, slow gait, diminished physical activities and unintentional weight loss; and pre-physical frailty is determined by the presence of one to two of the five criteria (Morley et al., 2013). The phenotypes of frailty and cognitive impairment are correlated with each other, and share several pathophysiological mechanisms with physical frailty. The concept of “cognitive frailty” was proposed to stimulate additional research in this area, emphasizing the key role of brain aging (Arts et al., 2016; Kelaiditi et al., 2013). Cognitive frailty is a heterogeneous clinical syndrome occurring in elderly individuals, excluding those with Alzheimer’s disease (AD) and other dementias, and is characterized by concurrent physical frailty and potentially reversible cognitive impairment (clinical dementia rating score (CDR) = 0.5) (Kelaiditi et al., 2013). Therefore, cognitive frailty is a type of pathological brain aging and a precursor to neurodegenerative processes.

Physical frailty and cognition are associated, however, the causal links between physical frailty and cognitive impairment are not clear (Ruan et al., 2015). Furthermore, information correlating physical frailty and biomarkers of AD in humans is uncommon, particularly regarding amyloid- β accumulation in the brain. Studies suggest that individuals who were physically active (Brown et al., 2013; de

Souto Barreto et al., 2015; Schultz et al., 2015) with increased gait speed (Del Campo et al., 2016; Wennberg et al., 2017) had significantly lower A β deposition compared with inactive persons with a poor gait. Moreover, the presence of β -amyloid peptides in muscle fibers was associated with inclusion body myositis and reduced muscle strength (Shtifman et al., 2010). Furthermore, to the best of the knowledge of the authors of the current study, no study has investigated the association between physical frailty and amyloid- β accumulation in the brain using ^{11}C -PIB PET to determine their role in frailty status under a dose-response relationship.

The objectives of this study were to examine the association between amyloid- β accumulation in the brain using a brain imaging biomarker, and physical frailty (weight loss, weakness, exhaustion, slowness, low physical activity) in older adults with mild cognitive impairment (MCI) and cognitive frailty. We hypothesized that amyloid- β accumulation in the brain is negatively associated with physical frailty status.

2. Methods

2.1 Study Sample

We selected 59 subjects participating in the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE) who were 65 years and older, lived in Seoul, and had no history of depression; degenerative neurologic disease; hospital admission in the past 12 months for any reason; illiteracy; or dementia. The inclusion criteria were: use of walking aids only if they enabled walking at least 10 m independently without using a mobility aid; and a CDR of 0.5. Of the 59 subjects included in the analyses undergoing ^{11}C -PIB PET, cognitive and physical performance tests, 11 were excluded due to low cognitive function (i.e., $\text{CDR} > 1.0$) and refusal of measurement. Thus, the remaining 48 subjects were selected to participate in this study (mean age, 75.1 ± 6.6 years; 73% female) (table 1). Physical frailty status was determined according to the five Cardiovascular Health Study (CHS) criteria defining physical frailty (Kelaiditi et al., 2013): unintentional weight loss, slowness, weakness, exhaustion, and low activity, which were scored 1 if present and 0 if absent. The total cumulative scores ranging from 0 to 5 were used to classify a participant as robust (score = 0), pre-frail (score = 1 to 2), or frail (score = 3 to 5). Cognitive frailty was defined as the simultaneous presence of physical frailty, as described above, and cognitive impairment, defined as a CDR of 0.5, and absence of concurrent dementia (Kelaiditi et al., 2013). The study protocol was approved by the Institutional Review Board of the Seoul National University Hospital and SNU-SMG Boramae Center, South Korea, approved the study. All participants provided written

informed consent. (SNUH IRB No. 26-2015-60)

2.2 Measurements

2.2.1 Frailty Definition

Frailty was assessed according to the previous criteria (Fried et al., 2001) for five frailty components operationally defined as: shrinking/weight loss of participants defined if the participant self-reported an unintentional weight loss of 4.5 kg in the last 12 months or when the body mass index was less than 18.5 kg/m². The participants' weakness was defined by low grip strength in each individual corresponding to gender and body mass index (BMI). Grip strength was measured using a hand-to-hand dynamometer (Takei Scientific Instruments, Niigata, Japan). This assessment protocol was repeated four times with a break in between. The average grip strength in kilograms was recorded, was less than or equal to the cutoff point used in the CHS. Exhaustion was defined based on the answers to two questions in the Center for Epidemiologic Studies Depression Scale (CES-D): "How often have you ever felt that everything you had done was useless in the last week?" and "How often have you ever felt that everything you had to do was not done in an appropriate mood last week?" Exhaustion was indicated by responses of "most of the time" and "often" (Collard et al., 2015). Slowness was defined as a low gait speed over 4 meters. Three lines were drawn horizontally on the measuring area. The start and end points were marked on the floor 1 meter from either mat end to avoid recording acceleration/deceleration phases. A speed < 0.8 m/s indicated frailty-related slowness

(Jung et al., 2016). The low physical activity corresponded to responses to International Physical Activity Questionnaire (IPAQ) items concerning low, middle, and high levels of physical activity. Responses describing low physical activity were indicative of frailty (Arts et al., 2016). A person was classified as “frail” when three or more criteria were met, “pre-frail” when one or two criteria were met, and “robust” when none of the criteria was met.

2.2.2 Functional performance

A short physical performance battery (SPPB) was used to assess the balance (ability to stand with the feet together in the side-by-side, semi-tandem, and tandem positions), gait speed (usual time to walk 4 m), and five chair-stand test (time to rise from a chair and return to the seated position five times without using arms). Each test received a performance score, with the total of 12 points comprising the chair stand test (4 points), balance test (4 points), and 4-m gait speed test (4 points). In the chair stand test the participants were initially seated. Upon verbal command, the participants stood and sat five times. A stopwatch was used to record the time in seconds to complete the task. Balance was measured in three tests, following an explanation. In the side-by-side stand test, feet were positioned together and balance was maintained for 10 s. In the semi-tandem stand test, each participant stood with a toe of the dominant foot touching the middle of the opposite foot for 10 s. In the tandem stand test, each participant stood with the toe of the dominant foot touching

the heel of the opposite foot for 10 s. The 4-meter gait test was used to assess the gait speed. The average time of two trials in the walking speed test were recorded. The three individual categorical scores were added to obtain a summary performance score for each participant (range, 0–12), with higher scores indicating better lower body function. A change in SPPB score of 1.0 point was considered significant (Perera, Mody, Woodman, & Studenski, 2006; Yoon et al., 2016).

The Timed Up and Go Test (TUG) is a widely used method for evaluation of basic mobility maneuvers. The TUG test protocol was based on a previous study (Yoon et al., 2017). It is performed as follows: Upon hearing a signal from a single rater, the subject rises from the chair without armrests, walks 2.44 meter in a linear path as quickly as possible, turns at a marker, walks back to the chair, and sits down.

2.2.3 Neuropsychological battery

A sensitive and validated neuropsychological test battery was used to assess the participants' cognitive function. The neuropsychological battery included the Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K), Korean version of Mini-Mental State Examination (MMSE-K) (Jeong et al., 2004) and CDR scales, which were evaluated by a single rater for all participants. The MMSE-K is commonly utilized to screen for dementia. The test consists of 11 questions and tasks, in a total of five cognitive domains: orientation (10 points), memory (6 points), attention (5 points), language ability (7 points) and

comprehensive/judgment (2 points). The highest score is 30 and a higher score indicates a higher level of cognitive function. The CERAD-K is comprised of five subtests derived from previously established cognitive tests: an executive domain of the verbal fluency test (0 – 24 points), a language domain of the Boston Naming Test (BNT) (0 – 15 points), a memory domain of the Word-List-Learning test (0 – 30 points) with delayed recall (0 – 10 points) and recognition (0- 10 points), and a visuospatial domain of the visual construction test (0 – 11 points). The total score of the CERAD-K was calculated by adding the six subtest scores (add, ref.). The CDR was calculated as the sum of all six items (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) in the CDR scale. The composite rating consists of five levels: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe) (Park et al., 2014).

2.2.4 ¹¹C-Pittsburgh Compound B-PET image acquisition and processing

All participants underwent simultaneous three-dimensional ¹¹C-Pittsburgh Compound B (PiB)-PET and 3D T1-weighted MRI scans with a 3.0 T Biograph mMR (PET-MR) scanner (Siemens) according to the manufacturer's approved guidelines. Prior to the scan, each participant received an intravenous dose of 555 MBq of PiB (range 450–610 MBq) and allowed to rest in a waiting room for 40 min. The PiB-PET data collected in list mode were processed for routine corrections such as uniformity, ultrashort echo time (UTE)-based attenuation, and decay corrections

and were reconstructed into a 256×256 image matrix using iterative methods (six iterations with 21 subsets). T1-weighted images were acquired in the sagittal orientation using the following characteristics: repetition time = 1670 ms, echo time = 1.89 ms, field of view = 250 mm, 256×256 matrix, and slice thickness = 1.0 mm. Further, the fluid-attenuated inversion recovery (FLAIR) and T2-weighted images were obtained for qualitative clinical readings.

All image processing and data analyses were performed using statistical parametric mapping (SPM) (SPM8 software; Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK) in MATLAB (MathWorks, Natick, MA, USA). The Static PiB-PET images were co-registered to an individual T1 structural image and the transformation parameters for the spatial normalization of the individual T1 image to a standard Montreal Neurological Institute (MNI) template were calculated. Using the IBASPM software, inverse transformation parameters were used to bring the Automated Anatomical Labeling (AAL) 116 atlas (Tzourio-Mazoyer et al., 2002) in a standard space to an individual space for each subject (resampling voxel size = $1 \text{ mm} \times 0.98 \text{ mm} \times 0.98 \text{ mm}$); the nongray matter portions of the atlas were individually masked using the cerebral gray matter segment image of each subject. Using the individual AAL116 atlas, the mean regional PiB uptake values from cerebral regions were extracted from the T1-coregistered PiB-PET images. The cerebellar gray matter was used as the reference region for the quantitative normalization of cerebral PiB uptake values due to its relatively low A β deposition (Lopresti et al., 2005). To measure PiB uptake in the

cerebellar gray matter regions, a probabilistic cerebellar atlas (Institute of Cognitive Neuroscience, UCL, UK; Cognitive Neuroscience Laboratory, Royal Holloway, UK) was brought into individual space as already described. Of the 28 anatomical structural regions in the cerebellar atlas, the cerebellar lobular regions (except for the vermis) were used to extract the mean cerebellar uptake values.

The AAL algorithm and a regional combining method (Reiman et al., 2009) were applied to set regions of interest (ROIs) to characterize PiB retention levels in the frontal, lateral parietal, precuneus/posterior cingulate cortex (PC/PCC), and lateral temporal regions, where prominent PiB retention was reported (Klunk et al., 2004). The standardized uptake value ratio (SUVR) values for each ROI were calculated by dividing the mean value of all voxels within each ROI by the mean cerebellar uptake value in the same image. Additionally, a global cortical ROI consisting of the four ROIs was defined and a global cortical SUVR was generated by dividing the mean value of all voxels of the global cortical ROI by the mean cerebellar uptake value in the same image (Figure 1). Global cerebral A β deposition was defined as the mean PiB retention value of the global cortical ROI.

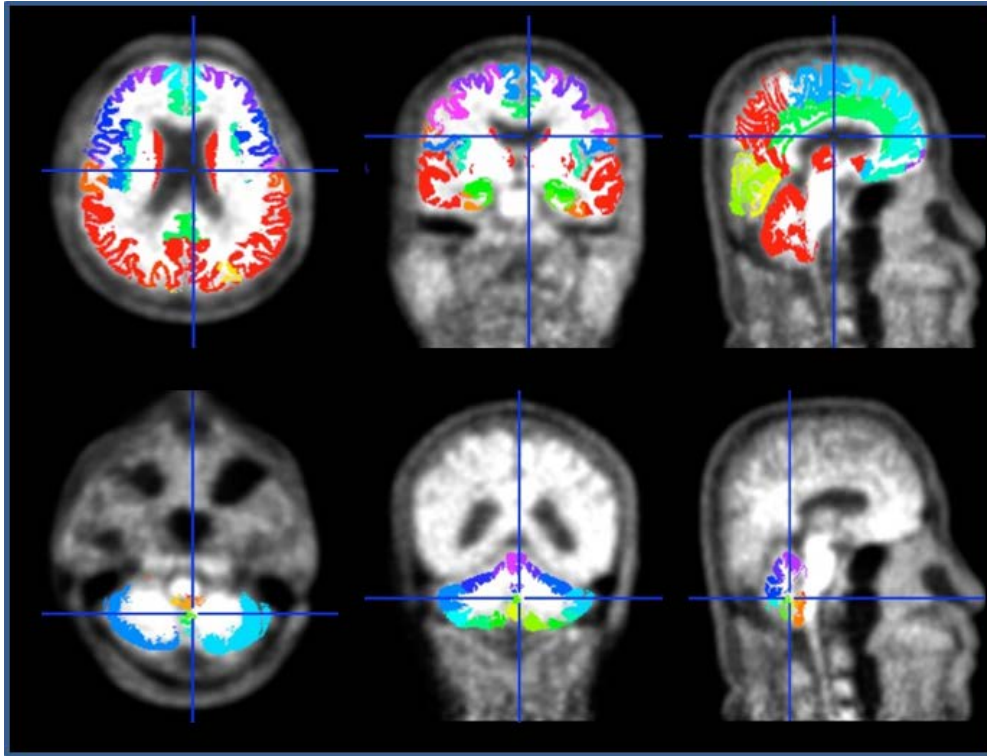


Fig 2. A representative image for regions of interest based on the AAL (automatic anatomic labeling) in an individual ^{11}C -PIB PET data. Using the published list of automatically labeled regions, the frontal ROI included bilateral frontal, anterior cingulate, middle cingulate, and insular cortex regions 3–34; the posterior cingulate-precuneus ROI included bilateral regions 35–36 and 67–68; the lateral temporal ROI included bilateral regions 79–90; the lateral parietal ROI included bilateral regions 59–65; the basal ganglia ROI included bilateral caudate, putamen, and globus pallidus regions 71–76; the medial temporal ROI included bilateral hippocampus, parahippocampal gyrus, and amygdala regions 37–42; and the cerebellar reference ROI included bilateral cerebellar crus I regions 91–92.

3. Statistical analyses

Statistical analyses were performed using SPSS 22.0 (IBM Corporation, Chicago, IL). Basic characteristics of the study sample were stratified by MCI and cognitive frailty groups were compared using the χ^2 test (categorical variables) and Student's t-test (continuous variables). The SUVR between subjects with MCI and cognitive frailty were determined using independent sample t-test for normally distributed variables (SUVR of frontal cortex, temporal cortex, parietal cortex, PC/PCC, hippocampus, basal ganglia, and global SUVR). The proportion of subjects with positive findings in visual analysis was calculated for each group and the percentage of cases in which visual analysis was consistent in ^{11}C -PiB PET images was calculated. Pearson correlation analysis was performed to test correlations between the regional and global SUVRs for ^{11}C -PiB PET. The threshold for statistical significance was set at a p-value < .05.

4. Results

4.1 Baseline Characteristics

At baseline, the mean age of the study participants was 75.1 (\pm 6.55 SD), 35 (73 %) were female, and the years of education were 9.4 (\pm 4.20 SD). Table 1 presents the characteristics of patients with MCI & Robust (43.8 % of total) and cognitive frailty (56.3 %). The differences among the two groups were significant in terms of slow gait velocity ($p=0.034$), weakness ($p=0.000$), exhaustion ($p=0.009$), and low activity level ($p=0.000$).). However, construction, mean (SD) and execution for CERAD-K showed significant differences between MCI and cognitive frailty groups (Table 1).

Table 6. Baseline Characteristics for Study Population

Variable	Full Sample, n = 48	Physical Frailty Status		<i>p</i> Value
		MCI + Robust, n = 21 (43.8%)	Cognitive Frailty, n = 27 (56.3%)	
Demographics :				
Age, mean (SD)	75.1 (6.55)	74.6 (5.65)	75.5 (7.28)	.644
Female, n (%)	35 (73%)	14 (67%)	21 (78%)	.285
Education, y, mean (SD)	9.4 (4.20)	9.1 (4.12)	9.7 (4.33)	.665
Frailty criteria, n (%) :				
Slow gait velocity	5 (10.2%)	0	5 (19%)	.034
Shrinking	4 (8.2%)	0	4 (15%)	.061
Weakness	13 (26.5%)	0	13 (48%)	.000
Exhaustion	7 (14.3%)	0	7 (26%)	.009
Low activity level	11 (22.4%)	0	11 (41%)	.000
Cognitive functioning :				
MMSE-DS (score), mean (SD)	24.3 (2.31)	24.7 (2.46)	24.0 (2.19)	.285
Cognitive impairment (MMSE < 23), n (%)	18 (36.7%)	6 (27.3%)	13 (48.1%)	.142
CDR (score), mean (SD)	0.5 (0.00))	0.5 (0.00)	0.5 (0.00)	
CERAD-K :				
Memory, mean (SD)	25.0 (5.74)	24.5 (5.97)	25.4 (5.63)	.622
Construction, mean (SD)	9.7 (1.44)	10.2 (1.33)	9.3 (1.44)	.039
Execution, mean (SD)	13.3 (4.58)	14.9 (4.59)	12.1 (4.25)	.035
Naming, mean (SD)	10.0 (2.43)	10.1 (2.37)	9.9 (2.53)	.816
Total Score, mean (SD)	58.0 (10.06)	59.7 (10.63)	56.6 (9.56)	.296

4.2 Quantitative analysis in MCI and Cognitive Frailty

The mean values of SUVR according to the brain regions of the two groups are summarized in Table 2. However, the SUVRs for ^{11}C -PiB PET were not significantly different between the MCI and cognitive frailty groups (Table 2).

Table 7. Comparison of SUVRs for ^{11}C -PIB in MCI and Cognitive Frailty subjects

	MCI	Cognitive Frailty	p
Frontal cortex	1.28 ± 0.41	1.47 ± 0.54	0.371
Temporal cortex	1.24 ± 0.35	1.40 ± 0.50	0.433
Parietal cortex	1.27 ± 0.43	1.44 ± 0.54	0.438
PC/PCC	1.43 ± 0.46	1.63 ± 0.60	0.424
Hippocampus	1.22 ± 0.21	1.27 ± 0.16	0.33
Basal ganglia	1.37 ± 0.37	1.43 ± 0.35	0.56
Global‡	1.32 ± 0.39	1.41 ± 0.40	0.429

‡ Arithmetic mean of frontal cortex, lateral temporal cortex, parietal cortex, precuneus/Posterior cingulate cortex (PC/PCC), and basal ganglia SUVR.

4.3 Visual analysis in MCI and Cognitive Frailty

The typical negative images in an MCI subject and the positive images in a patient with cognitive frailty are shown in Fig. 1. After adjusting the window level of ^{11}C -PiB PET with reference to the cerebellar cortex, each case failed to show a significantly higher white matter uptake compared with the gray matter uptake between the MCI and cognitive frailty groups. Overall, all participants showed identical results based on visual analysis of both PET images. (Fig 2).

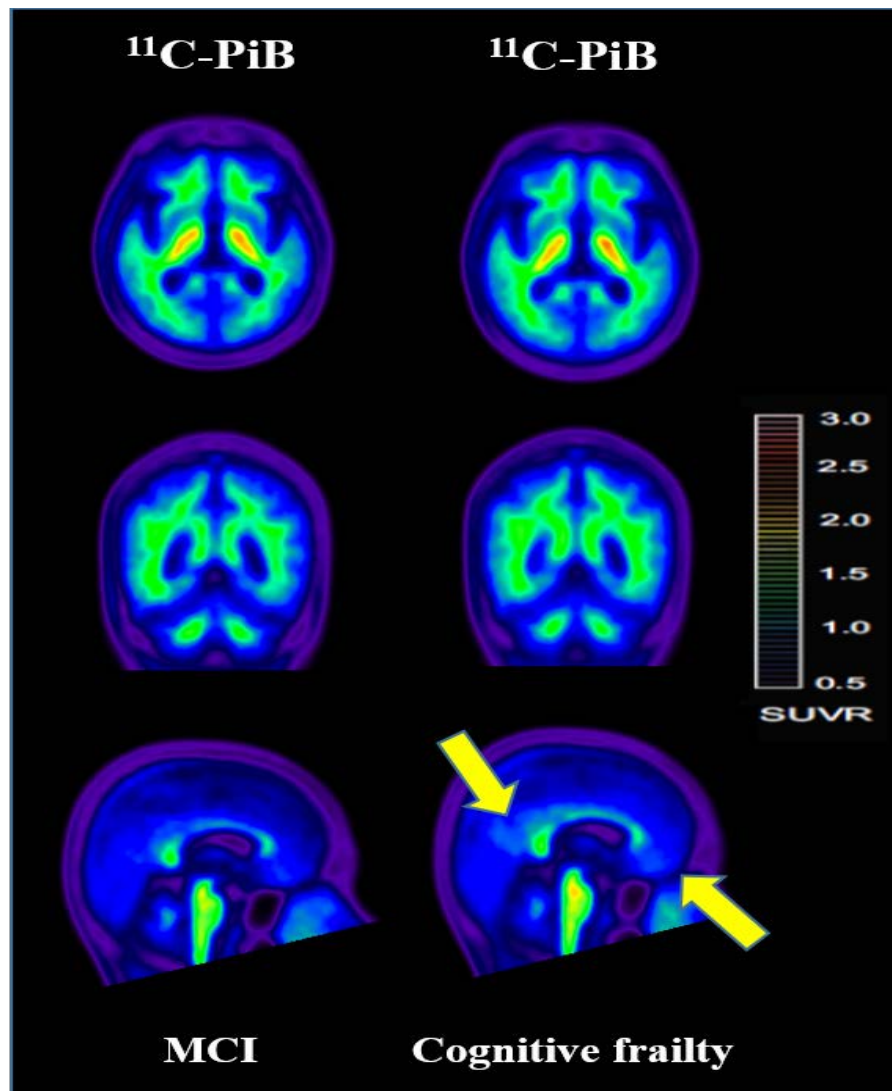


Fig 3. Representative Images of [11C]PiB PET for cerebral amyloid burden of the same MCI and the same Cognitive Frailty patient. Images scaled to the same SUVR are shown. Left row: negative amyloid scan, and Right row: positive amyloid scan. SUVR = standardized uptake value ration.

4.4 Quantitative analysis the comparing global SUVR in MCI and cognitive frailty

Comparisons of SUVRs for ^{11}C -PiB PET in each population are illustrated in Fig. 3. However, there was no significant difference in the SUVR of ^{11}C PiB PET between MCI and cognitive frailty groups of patients. In addition, no significant differences were detected in the frontal cortex-to-white matter SUV ratios in MCI or cognitive frailty groups of patients

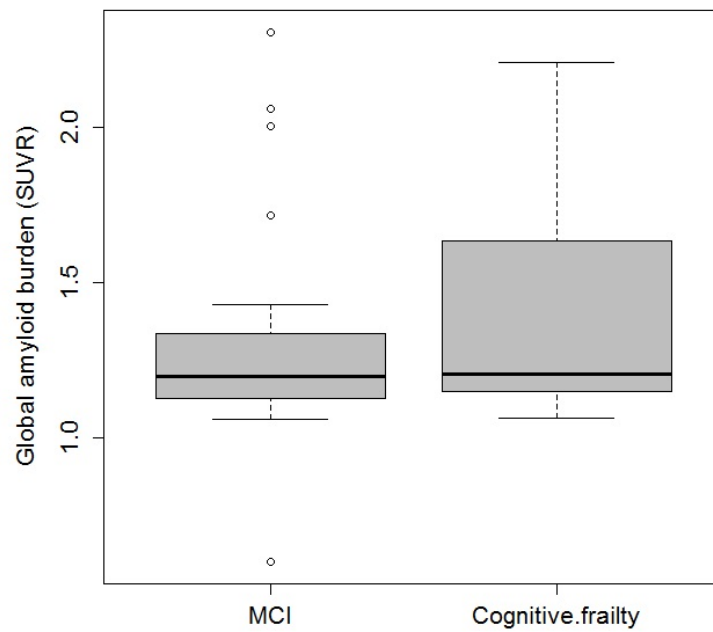


Figure 4. Box plots comparing global SUVR assessed ^{11}C -PiB PET in MCI and cognitive frailty participants. Global amyloid burden (SUVR) represents a mean of frontal cortex, lateral temporal cortex, parietal cortex, Posterior cingulate cortex/precuneus (PC/PCC), and basal ganglia SUVR. MCI = mild cognitive impairment, SUVR=standardized uptake value ratio.

4.5 Association between SUVR by brain regions and different measures of Physical function

The global amyloid burden (SUVR) was significantly linked to gait speed ($p=.046$). Basal ganglia ($p=.021$), PC/PCC ($p=.012$), parietal cortex ($p=.045$), and temporal cortex ($p=.049$) were significantly linked to gait speed, unlike frontal cortex and hippocampus. In addition, basal ganglia and PC/PCC were significantly linked to SPPB ($p=.047$, $p=.043$; respectively) and TUG ($p=.033$, $p=.026$; respectively) (Table 3).

Table 8. Association Between Presence of mean values of SUVR by brain regions and Different Measures of Physical function.

	SPPB		TUG		Gait speed		Grip strength	
	β	P	β	P	β	P	β	P
Frontal cortex	-0.253	.082	0.212	.148	0.252	.084	-0.104	.481
Temporal cortex	-0.261	.074	.0238	.104	0.285	.049	-0.127	.389
Parietal cortex	-0.249	.088	0.243	.096	0.291	.045	-0.164	.264
PC/PCC	-0.294	.043	0.320	.026	0.359	.012	-0.196	.288
Hippocampus	-0.260	.074	0.173	.241	0.187	.204	-0.055	.708
Basal ganglia	-0.289	.047	0.309	.033	.333	.021	0.034	.821
Global‡	-0.205	.161	0.272	.062	0.289	.046	-0.078	.596

β, completely standardized regression coefficient.

4.6 Association between SUVR by brain regions and physical frailty

The SUVR values of all the brain regions were significantly linked to weakness as follows: global amyloid burden ($p=.009$), frontal cortex ($p=.010$), temporal cortex ($p=.008$), parietal cortex ($p=.023$), PC/PCC ($p=.009$), hippocampus ($p=.008$), and basal ganglia SUVR ($p=.009$) (Table 4).

Table 9. Association Between Presence of mean values of SUVR by brain regions and Each Criterion of the Frailty index

	Weight loss		Exhaustion		Weakness		Slowness		Low activity	
	β	P	β	P	β	P	β	P	β	P
Frontal cortex	-.149	.312	.072	.627	.367	.010	-.033	.821	-.023	.877
Temporal cortex	-.138	.350	-.010	.345	.377	.008	-.003	.986	-.020	.895
Parietal cortex	-.179	.223	.076	.609	.328	.023	.000	.997	-.035	.811
PC/PCC	-.144	.327	.049	.742	.372	.009	.030	.837	-.017	.911
Hippocampus	.018	.905	-.086	.563	.377	.008	.030	.841	-.010	.946
Basal ganglia	-.104	.482	-.047	.753	.374	.009	.011	.943	-.030	.842
Global‡	-.148	.316	.033	.823	.371	.009	.002	.991	-.025	.864

β , completely standardized regression coefficient.

5. Discussion

In visual analysis, the cortical uptake of ^{11}C -PiB scans was not significantly different between the groups. Although quantitative analysis showed that ^{11}C -PiB global SUVR did not significantly vary from each other in patients with MCI and cognitive frailty, these results are in agreement with previous studies showing cortical SUVR with ^{11}C -PiB amyloid PET in MCI and AD (Byun et al., 2017). However, few studies showed that A β deposition occurred in normal elderly subjects, who may subsequently develop signs of MCI and ultimately develop AD. Postmortem analysis demonstrates the characteristic abundance of A β plaques in specific brain areas of AD patients. Recent PET studies using ^{11}C -PiB in elderly normal subjects support the existence of a preclinical AD stage in which A β plaques are found in discrete brain regions based on significant radioligand retention, approaching levels seen in AD subjects, in about 10% of the elderly control subjects (Mathis, Lopresti, & Klunk, 2007).

We observed the strongest association between ^{11}C -PiB PET SUVR values globally (temporal cortex, parietal cortex, PC/PCC, basal ganglia) and gait speed, SPPB (PC/PCC, basal ganglia), and TUG (PC/PCC, basal ganglia). Similarly, studies have shown that ventricular enlargement in the temporal horn is associated with worse gait parameters, including variation in stride time and gait speed (Wennberg et al., 2017). In addition, a recent MAPT study reported that the usual pace of walking speed is associated with amyloid deposition assessed by PET scans (Del Campo et al., 2016). These authors found a significant association between amyloid in the posterior

and anterior putamen, occipital cortex, precuneus, and anterior cingulate and slow gait speed. Gait speed is a marker of frailty phenotype, which is attributed to age-related reduction in physiologic reserve (Fried et al., 2001). Studies have consistently shown that gait speed predicts major health-related events, including future disability, hospitalization, and death (Cesari et al., 2005). Slow gait speed possibly reflects a state characterized by multisystemic changes that may increase the susceptibility of brain to AD pathology and subsequent damage.

A major contribution of this study involves the assessment of global SUVR in participants with cognitive frailty. In the present study, the association between brain amyloid- β and weakness was reflected by the SUVR values of all the brain regions. Recent studies have shown that muscle weakness based on handgrip strength evaluation predicts exhaustion, functional decline, morbidity and mortality. In fact, frailty is probably six-fold higher among persons with reduced grip strength (Houles et al., 2012). Muscle weakness has also been indicated as one of the initial manifestations of frailty (Houles et al., 2012). Nevertheless, in the absence of studies investigating the association between brain amyloid level and chair rise, it is impossible to compare our results with the published literature. Based on evidence showing that patients with AD exhibit increased levels of amyloid deposition in brain and muscle(13), and that intracellular β -amyloid in muscle fibers is associated with reduced muscle strength (9) (and potentially sarcopenia), our previous study using data from the MAPT population found negative associations between gait speed and regional brain amyloid (14). We hypothesized that higher amyloid accumulation in

the brain is associated with frailty index. Thus, it is not unexpected that amyloid- β levels in different brain regions might be associated with only weakness.

The present study is limited by a relatively small sample size including subjects at a single institution. A multi-institutional study involving a larger number of subjects is required to corroborate the results of this study.

Overall, this study showed that the amyloid levels in the brain cortices or regions were not associated with each other in patients with MCI and cognitive frailty. Nevertheless, the present study found a correlation between brain amyloid- β levels and weakness, based on the SUVR values of different brain regions. Further, an association existed between the global SUVR (temporal cortex, parietal cortex, PC/PCC, and basal ganglia) and gait. However, additional studies are needed in order to confirm or refute our findings. Further research is needed to elucidate the neural mechanisms underlying this association, ideally involving exercise interventions and study designs that facilitate analysis of causal relationships.

III. Conclusion

In this dissertation, two study of experimental were investigated. The first intervention study is to determine the effect of high-speed resistance exercise training on cognitive function and physical performance in older adults with cognitive frailty. Second study, examine the association between brain amyloid- β accumulation as assessed by a brain imaging biomarker and Physical frailty (weight loss, weakness, exhaustion, slowness, low physical activity) in older Adults with mild cognitive impairment (MCI) and cognitive frailty. To achieve our objective, patients with cognitive frailty were included in this controlled trial study on the basis of the following: 1) CDR of 0.5 with the absence of concurrent dementia; 2) At least one CHS criterion of physical frailty (inclusion frailty and pre-frailty); and 3) Ability to walk 10-m without requiring a walking aid. The following is a summary of the two research results conducted to achieve the purpose of the research.

1) Our results revealed that high-speed resistance exercise group showed significant improvement in cognitive function test (processing speed and executive function, both $p \leq 0.05$), physical function (SPPB, TUG, gait speed, both $p \leq 0.05$), and muscle strength (grip strength, knee extension strength, both $p \leq 0.05$). However, no significant ($p > 0.05$) change in frailty score and frailty prevalence was observed in both intervention and control group.

2) Second, any of mean cortical (regions of interest) and each regional SUVRs

(frontal cortex, lateral temporal cortex, parietal cortex, precuneus/Posterior cingulate cortex (PC/PCC), hippocampus, basal ganglia, and global SUVR) were associated to gait speed, TUG, SPPB, and weakness.

The overall conclusions and suggestions are as follows: High-speed resistance exercise training is effective in improving cognitive function and physical performance in older adults with cognitive frailty. Therefore, it is feasible to use high-speed resistance exercise training to effectively reduce the level of frailty states and cognitive impairment in older adults with cognitive frailty in community and primary care setting. Also, any of cortical or regional brain amyloid load were not associated between each other in MCI group and Cognitive frailty group. Nevertheless, as another result in the present study, the association between brain amyloid- β and weakness were found that SUVR values of all brain regions. Also, association between the global SUVR (temporal cortex, parietal cortex, PC/PCC, basal ganglia) and gait parameter. However, the debate is far from closed, and future studies in this field should be done in order to confirm or refute our findings. More research is needed to elucidate the neural mechanisms underlying this association, ideally involving exercise intervention study designs that might enable cause-effect conclusions.

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국문초록

노쇠(Frailty)'란 신체적 기능 및 활동력 저하 등의 병적상태를 반영하는 임상적 지표이며 이러한 상태는 나아가 낙상 및 골절, 인지기능 저하, 대사질환, 심뇌혈관 질환의 위험률을 증가시키고 궁극적으로 사망률을 증가시키는 위험인자로서 특히 노인인구의 수명과 웰니스를 결정짓는 중요 임상 상태이다. 신체적 노쇠와 인지기능의 장애는 강한 상호작용을 나타내고 있으며, 공통적으로 일어나는 위험 요인으로 체중감소, 보행속도 감소, 낮은 근력과 좌식생활습관 그리고 비만, 근감소증 (sarcopenia)등을 많은 연구들에서 제시하고 있다. 이처럼 신체적 노쇠와 인지기능의 장애는 위험요인을 공유하기 때문에 신체노쇠와 인지장애가 모두 있는 노인에서 나타날 수 있는 다양한 임상군을 정의한 것으로 인지노쇠(cognitive frailty)를 개념화 하였다. 인지노쇠는 신체노쇠와 경도인지장애(CDR=0.5)가 공존해있으면서 알츠하이머병 등 기타 치매가 없는 상태로 퇴행성신경 질환으로 진행할 수 있는 전구기 상태를 의미하지만 한편으로는 개선 가능한 단계를 의미한다. 이에 1960년대까지만 해도 성인기 이 후 신경계는 변화하기 어렵다는 가설이 주를 이루었으나 최근에는 중추신경계에 손상을 입은 후에도 주위 환경이나 병변에 맞도록 대뇌피질의 기능과 형태가 변할 수 있다는 의미의 신경가소성(neuroplasticity)이 대두되고 있다. 현재까지는 노쇠가 치매 발병에 명확한 원

인이 되는지는 불확실한 상태이지만, 신체 노쇠가 독립적으로 인지기능 저하를 가져오는지, 아니면 치매병리가 신체노쇠를 동반하는지는 확실하지 않은 상태이다. 결과적으로 인지노쇠의 발병을 예방하기 위한 저항성 운동 중재의 시기적절한 초기개입 및 관리가 매우 중요하며 그와 더불어 신체적 노쇠와 인지기능 장애 사이의 관련성을 밝힘으로 경도인지장애와 치매로 인한 기능저하 속도를 늦추는 것이 중요하다. 따라서 본 연구의 목적은 다음과 같은 세부목표를 통해 복합적으로 규명하고자 하였다. Aim 1. 인지노쇠 (cognitive frailty) 노인을 대상으로 저항성 운동이 노쇠상태와 신체적 기능 그리고 인지기능에 미치는 효과를 검증하고자 하며, Aim 2. Brain imaging을 통해 아밀로이드 플라그(amyloid plaques) 형성에 관여하는 아밀로이드-베타(amyloid- β , A β)의 축적이 인지노쇠군(cognitive frailty)과 경도 인지장애군(mild cognitive impairment)에서 관계성과 아밀로이드-베타의 (amyloid- β , A β) 축적이 신체노쇠와 신체적 기능에 미치는 영향을 밝히는데 있다. 본 연구의 두 가지 주제에 대한 결과 중 첫 번째, 인지노쇠 노인을 대상으로 저항성 밴드를 이용한 16주간의 High-speed Power Training은 인지기능 (processing speed and executive function, 각각 $p \leq 0.05$), 신체적 기능 (SPPB, TUG, gait speed, 각각 $p \leq 0.05$), 그리고 상·하지 근력 (grip strength, knee extension strength, 각각 $p \leq 0.05$)에서 컨트롤 그룹과 비교하여 통계적으로 유의하게 증가하였으나 노쇠 단계와 유병율에서는 유의한

증가가 나타나지 않은 것을 확인하였다. 두 번째, 인지노쇠 그룹과 경도인지장애 (Mild Cognitive Impairment) 그룹에서 뇌 영상을 통한 각 부위별 (전두엽, 외측두엽피질, 두정엽, 소엽/후측대상피질, 해마, 기저핵 그리고 global SUVR) SUVRs (Standardized uptake value ratio) 값은 그룹간 통계적으로 유의하지 않았으나, 뇌 각각의 구역별 SUVR 값은 보행속도와 TUG, 그리고 SPPB, 노쇠 척도에서는 weakness (각각 $p \leq 0.05$)에서 통계적으로 유의한 상관관계를 나타낸 것을 볼 수 있었다. 이상의 결과를 통해 본 연구의 결론은 다음과 같다. 16주간의 저항성 운동은 인지노쇠 노인들의 인지 기능과 신체기능을 향상시키는데 효과적인 것을 확인할 수 있었으며, 뇌 영상을 통한 아밀로이드 베타의 축적 정도는 인지노쇠 그룹과 경도인지장애 그룹에서 통계적으로 유의한 차이를 나타내진 않았지만 더 중요한 것은 아밀로이드 베타의 축적이 신체적 기능과 weakness에 부정적인 영향을 준다는 것을 알 수 있었다. 비록 본 연구에서는 피험자의 수가 작다는 점과 운동중재 기간이 비교적 짧다는 제한 점을 가지고 있지만 향후 이러한 점들을 보완하여, 뇌에 축적된 아밀로이드 베타가 신체적 노쇠와의 부적 상관관계를 가진다는 것과 추후 운동 중재를 통해 치매를 예방 또는 중재할 수 있다는 결과를 도출해 낼 수 있을 것이라 사료된다.

주요어: Amyloid imaging, 아밀로이드 베타, 인지노쇠, 노쇠, 경도인지장애,

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